REMARKS/ARGUMENTS

Claims 1, 2, 6-8, 11, 12, and 14-17 are pending in the above-identified application. Claims 1 and 7 have been amended to point out the invention with greater particularity. Support for the amendment is set forth in the remarks below. No new matter has been added by the amendments.

All claims currently pending stand rejected as allegedly unpatentable under 35 U.S.C. § 103. Reconsideration and withdrawal of these rejections are respectfully requested in view of the amendments above and the remarks and arguments set forth below.

Rejections Under 35 U.S.C. §103(a)

Claims 1, 2, 6, 11, 12 and 14-17

Claims 1, 2, 6, 11, 12 and 14-17 remain rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Corr *et al.* (*J. Exp. Med.* 184:1555-1560, 1996; hereinafter "Corr (1996)") in view of Corr *et al.* (*J. Immunol.* 159:4999-5004, 1997; hereinafter "Corr (1997)"). The Examiner alleges Corr (1996) teaches intramuscular injection of a viral protein antigen mixed with naked plasmid DNA encoding B7.1 or B7.2 co-stimulatory molecule. In addition, the Examiner admits that Corr (1996) does not teach that muscle cells at the site of injection present antigen to the immune system, but rather professional bone marrow-derived APCs present the antigen that results in a CTL response to the antigen. Still further, the Examiner admits that Corr (1996) do not teach separate administration of a protein antigen comprising one or more T cell epitopes separately from the plasmid DNA encoding B7.1 or B7.2 co-stimulatory molecule to closely adjacent sites.

Contrary to the allegation of the Examiner Corr (1996) does not teach intramuscular injection of a viral protein antigen mixed with naked plasmid DNA encoding 7.1 or B7.2. Instead, Corr (1996) teaches the injection of a naked plasmid DNA encoding a viral protein having epitopes for two different haplotypes to distinguish whether somatic cells or the tissue surrounding the injection site or the circulating antigen presenting cells present the encoded antigen expressed by transfected muscle cells. See the Summary on page 1555 and

page 1556, left column, lines 30 - 35; and paragraph 11 of the Berzofsky Declaration . The use of a peptide, polypeptide or protein in the immunization process in not disclosed or suggested in Corr (1996). The reference merely reports that somatic cells in the area of the injection do not present antigen, but that circulating antigen presenting cells are responsible. (See paragraph 11 of the Berzofsky Declaration.) In addition, no disclosure or suggestion of the use of a naked DNA plasmid encoding a co-stimulatory molecule can be found in Corr (1996). (See paragraph 12 of the Berzofsky Declaration.)

The Examiner alleges Corr (1997) as teaching that co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response. In addition, the Examiner alleges that Corr (1997) teaches intramuscular or intradermal injection of protein antigen mixed with plasmid DNA encoding B7.1 or B7.2 co-stimulatory molecule and that Corr (1997) teaches that expression of the MHC class I restricted epitope in the same cell as the costimulatory ligand is not imperative for T cell priming, but *in vivo* a T cell cannot be effectively primed with a cognate signal from a peripheral somatic tissue if a second signal stimulus is not available in the immediate vicinity, for example in the same muscle. The Examiner alleges that Corr (1997) teaches that *in vivo* transfection of peripheral somatic tissues with plasmids encoding costimulatory ligands not only enhanced immune responses to antigen expressed by gene vaccination, but also dramatically increased the immune response to co-injected protein antigens. In addition, the Examiner alleges that Corr *et al* (1997) teach that by increasing the density of membrane-bound costimulatory molecules, naked plasmid DNA injection can boost immune responses to soluble protein antigen in a manner analogous to conventional adjuvants, but without apparent systemic side effects. Still further, the Examiner alleges that Corr *et al* (1997) teach that the plasmid DNA were constructed with a promoter regulatory element for high expression.

Applicants must again respectfully disagree with the Examiner's interpretation of the teachings of Corr (1997). Many of the above statements taken from Corr (1997) have been taken out of context and only provide a limited view of the teachings of Corr (1997). For example, as set forth above the Examiner has alleged that Corr (1997) teaches that co-expression

of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response. This statement is only part of a paragraph that discusses the direct injection and expression of different plasmid DNAs as ectopic transgenes in peripheral somatic tissues. The discussion further states that direct *in vivo* transfection allowed not only for the selective expression of a single minimal antigenic epitope in the context of the animal's endogenously synthesized MHC class I molecules, but also for the functional expression of various membrane bound co-stimulator molecules on the host's own cells. The studies disclosed demonstrate that co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted Ag is sufficient to prime a CTL response in the absence of $CD4^+$ T cell help. (See page 4999, right column, lines 6 through 18.) The discussion does not relate to the administration of a plasmid expression B7-1 in combination with a soluble antigen. (See paragraph 15 of the Berzofsky Declaration.)

In addition, Corr (1997) disclose the injection of animals with the B7-1 or B7-2 vectors in either the ipsilateral or the contralateral quadriceps as the vector encoding antigen to determine whether the co-stimulator plasmid acted locally or exerted a global nonspecific systemic immunostimulatory effect. The experiments described in Fig. 4, page 5002, showed that the enhancement of a CTL or antibody response depended on the presence of the costimulatory plasmid mixed together with the antigen-encoding plasmid and administered together at the same site not administered separately at adjacent sites. (See description of experiments at page 5001, right column, lines 12 - 16 and Fig. 4.) Still further, Corr (1997) disclose the injection of the plasmids encoding B7-1 or B7-2 with ovalbumin protein induced an antibody response only when they were mixed together and injected at the same site. (See Fig. 5 and page 5001, right column, lines 31 - 35.) When considered together these data presented in Corr (1997) clearly demonstrate that the reference does not disclose or suggest that co-injection of the plasmid encoding a co-stimulatory B7 molecule and a peptide or protein is the same as injecting the plasmid and the peptide or protein separately at closely adjacent sites. Furthermore, the experiment in which protein antigen is mixed with DNA plasmid encoding B7-1 (Fig. 5) demonstrates only an antibody response, not a CTL response. No experiment is provided nor is there a suggestion wherein a peptide epitope is injected even at the same site as a DNA plasmid

encoding B7-1, let alone at closely adjacent sites. Still further, no experiment is provided to look at a CTL response after injecting the mixture of protein and DNA. The data particularly do not support the Examiner's assertion that Corr (1997) discloses or suggests that the method as claimed can result in the induction of an antigen specific cytotoxic T cell response. (See paragraph 15 and 19 of the Berzofsky Declaration.)

In order to further expedite prosecution of this aspect of the invention claims 1 and 7 have been amended for clarity. Specifically, claims 1 and 7 have been amended to recite "[a] method for eliciting an antigen specific cytotoxic T cell response in a subject." Support for this amendment can be found in the specification at, for example, page 15, lines 15-28, pages 21 and 22, and the Examples beginning at page 61.

Further, it is alleged by the Examiner that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered the viral protein antigen taught by Corr (1996) or the CTL peptide epitope taught by Corr (1997) separately from the naked plasmid DNA encoding B7.1 and/or B7.2 co-stimulatory molecule to closely adjacent sites as taught by Corr (1997). The Examiner has asserted that motivation for one of ordinary skill in the art to do this is provided because co-administration or separate administration to closely adjacent sites are equivalent methods. In addition, the Examiner has asserted that the artisan of ordinary skill in the art would have motivation because the method would provide for convenience and standardization between administrations, because the same naked plasmid DNA preparation administered separately to a closely adjacent site could be used for co-ordinate immunizations with different protein or peptide antigens, and because Corr (1997) teaches that co-expression of B7-1 in the vicinity of a minimal MHC class I-restricted antigen is sufficient to prime a CTL response, including wherein the antigen is a protein antigen. Claim 14 has been included in this rejection because the Examiner alleges that the peptide antigen administered separately to a closely adjacent site is "administered to the subject in a sequential vaccination protocol."

Applicants must again point out that Corr (1996) does not disclose the administration of a soluble viral protein antigen, but instead disclose the administration of a plasmid that encodes a viral protein antigen epitope. In addition, Corr (1997) clearly discloses that the administration of a naked plasmid encoding a co-stimulatory B7 molecule together with a plasmid encoding an antigen or an epitope of an antigen is not the same as injecting the co-stimulatory plasmid together with the protein antigen. In the case of the two plasmids a CTL response is induced and in the other an antibody response is induced. It should be noted in particular that in both cases the immune response was only induced when the two plasmids or the plasmid encoding B7 and the polypeptide were injected mixed together at the same site. As such, Applicants can not find any support for the allegation of the Examiner that injection of a mixture of two components, the two plasmids or the plasmid expressing B7 and the polypeptide, can be equated with injection of the components separately at closely adjacent sites. (See paragraphs 15,16, 19 and 20 of the Berzofsky Declaration.)

Claims 7 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Corr (1996) in view of Corr (1997) as applied to claims 1, 2, 6, 11, 12 and 14-17 above, and further in view of WO 99/45954 A1. The Examiner's summaries of Corr (1996) and Corr (1997) are presented above. The Examiner does not believe that the combination of the Corr references teach a viral antigen from HBV, HCV, HSV or HPV. But, the Examiner alleges that WO 99/45954 teaches that epitopes on antigens such as HBV, HCV, HPV and HSV are useful in pharmaceutical compositions for both therapeutic and diagnostic applications. WO 99/45954 A1 is also alleged by the Examiner to teach that the peptides bind to class I HLA molecules, *i.e.*, are about 8-11 amino acid residues in length. The Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have utilized the epitopes or protein antigens taught by WO 99/45954 A1 in the method taught by the combined references. Motivation for this combination is alleged by the Examiner to be provided by the combined Corr references teaching an improved method for generating an effective immune response, and WO 99/45954 A1 teaching that epitopes on antigens such as HBV, HCV,

HPV and HSV are useful in pharmaceutical compositions for both therapeutic and diagnostic applications.

Applicants must again respectfully disagree with the rejection of claims 7 and 8 on the above basis. In particular, as above the combination of the Corr references do not teach or suggest that separate administration of a naked plasmid encoding a co-stimulatory molecule and a polypeptide having a T cell epitope at separate closely adjacent sites will induce an antigen specific immune response much less an antigen specific cytotoxic T cell response. (See paragraph 18 of the Berzofsky Declaration.) Further, as above, co-administration at the same site of two plasmids one encoding the co-stimulatory molecule and the other encoding a polypeptide teaches nothing about the co-administration at the same site of a plasmid encoding a co-stimulatory molecule and a polypeptide. Corr (1997) teaches that the immune response induced in each case is different. In the first a CTL response can be induced and in the second and antibody response is induced. The claims as amended are directed to methods for the induction of an antigen specific CTL response by administering the naked plasmid encoding the co-stimulatory B7 molecule and the polypeptide having a T cell epitope in separate closely adjacent sites. As such, this method is not disclosed or suggested either separately by the Corr (1996) or Corr (1997) references or by their combination. Given that the primary references do not disclose or suggest the independent claim, the combination with WO 99/45954 can not disclose or suggest the invention encompassed by dependent claims 7 and 8. Applicants therefore respectfully request the Examiner reconsider and withdraw the rejection of claims 7 and 8 as unpatentable over Corr (1996) and Corr (1997) in view of WO 99/45954.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 2, 6-8, 11, 12, and 14-17 under 35 U.S.C. § 103 in view of the above amendments and remarks.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 17 October 2007

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